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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/469,492	06/06/95	WEINER	H	1010/16959-U

HM12/0329

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EXAMINER	
DUFFY, P	
ART UNIT	**PAPER NUMBER**
1645	22

DATE MAILED: 03/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/469,492	Werner et al
Examiner	**Group Art Unit**
Duffy	1645

☒ Responsive to communication(s) filed on 129(a) + Amendment 12/10/99.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 37-39, 42-49, 52-57, 59, 61, 62, 64, 65 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 37-39, 42-49, 52-57, 59, 61, 62, 64 + 65 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on 12-10-99 has been entered.

2. Claims 37-39, 42-49, 52-57, 59, 61, 62, 64 and 65 are pending and under examination. Claims 60 and 63 having been canceled.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. The rejection of claims 37-39, 42-49, 52-57, 59, 61, 62, 64 and 65 under 35 U.S.C. 112, first paragraph is maintained for reasons made of record for claims 37-58 in Paper No. 6, mailed 12-31-96 and maintained in each office action thereafter.

Applicants' arguments have been again carefully considered but are not persuasive. Applicants allege that nothing less than double blind placebo controlled studies in humans will satisfy the examiner. This misrepresents both the facts at hand and the claimed subject matter. The issue at hand is whether the written description in applicants specification and the evidence therein, combined with the evidence submitted provides for enablement for the claimed subject matter. The instant claims are drawn to treatment of an autoimmune disease in a human by administering by nose or mouth an effective amount for treating said disease a composition comprising a bystander antigen wherein said bystander antigen is not an autoantigen in said human and wherein said bystander antigen is not insulin. The specification defines "treatment" to include both prophylactic treatment to prevent an autoimmune disease as therapeutic

suppression or alleviation of symptoms after the onset of such autoimmune disease see specification pages 9-10, bridging paragraph). It is noted that applicants are specifically claiming treatment of a human disease and specifically exclude autoantigens. Table 1 on page 19, exemplifies the diseases and corresponding bystander antigens. Many of the bystander antigens illustrated herein are specifically excluded by the language of the claims which state that the bystander antigen is not an autoantigen or not insulin. As previously stated in the record, glutamic acid decarboxylase (GAD), heat shock protein (see Cohen et al of record), are autoantigens for Type I diabetes, leaving only glucagon as a bystander antigen to fall within the scope of the claims. Table 1, indicates that multiple sclerosis can be treated with myelin basic protein (MBP) or proteolipid protein (PLP). Both of these are autoantigens (Cohen et al, Autoimmune Disease Models, page 2) and T-cell reactivity to both of the antigens have been demonstrated in multiple sclerosis patients (Hafler et al., J Immunology, 139:68, 198) and were recognized autoantigens at the time of applicants invention. Thus, no working embodiments are left for the treatment of multiple sclerosis. Applicants' evidence with respect to PLP and MBP have no merit in this application because these bystander antigens are in fact autoantigens and are specifically excluded by applicants claims. Applicants reliance and emphasis on this evidence, and subsequent results from further studies on MBP, insulin etc. are irrelevant to the claims at hand and is an attempt to misdirect the issues for this claimed invention. Back again to Table 1, it is again noted that both collagen (Paul ed. Fundamental Immunology, 19 , page 848, human T-cell response to collagen in rheumatoid arthritis) and heat shock protein are autoantigens. Thus, no working embodiments of bystander antigens that are not autoantigens, are set forth for treatment of rheumatoid arthritis. Back again to Table 1, the autoimmune disease uveoretinitis also involves the autoantigens: S-antigen and interphotoreceptor retinoid

binding protein (IRBP). Autoantigens are art defined as (self antigen) which is an antigen that is a normal constituent of the body and against which an immune response may be mounted in the same individual (page 17, Herbert et al, The Dictionary of Immunology, fourth edition Academic Press, 1995) and an immune response is defined as a specific to an antigen which is inclusive of both cellular immunity (i.e. T-cell) and humoral immunity (B-cell) (page 89, Herbert et al.). Clearly, the only autoimmune disease remaining, without a bystander antigen being an autoantigen is type 1 diabetes and glucagon. Glucagon itself is not contemplated as a bystander antigen for any other autoimmune disease. The specification teaches but a single example of an autoimmune disease and corresponding bystander antigen which is not an autoantigen. The written description of a single bystander antigen and corresponding single disease to be treated does not provide a written description to enable the scope of the claimed subject matter for reasons already made of record. Moreover, the issue of enablement with respect to treatment of humans is highly relevant in this subject area since treatment of humans is that which is specifically claimed. Not only is the disease model particularly important, but the examiner has established for the record that the disease model should be predictable and reproducible for the treatment of humans. The teachings of the specification are limited to oral administration of glucagon to suppress insulitis in NOD mice model. The ability to then "treat" Type I diabetes in humans by oral or nasal administration is the issue, as it flows from the showings of the specification for the NOD mouse model. The specification specifically defines that "treatment" encompasses prophylaxis and prevention. Such is not enabled by this specification in humans for the reasons already made of record. For example, to provide for prophylaxis, one skilled in the would have to be able to determine at which point to administer oral glucagon in humans. The specification has not set this forth, no guidance as to this aspect is presented at all in the

specification. Unlike animal models, the disease trigger in human is not specifically timed and thus prophylaxis of disease can not be accomplished in humans. Applicants' arguments notwithstanding, the art of treatment of diabetes does not recognize any specific time point for which a composition can be administered and prevent Type I diabetes and thus applicants reliance on arguments that the skilled artisan could determine such, are not persuasive. Suppression of insulitis by oral administration of glucagon, is not commensurate in scope with the claims and does not support nor enable prophylaxis or prevention of disease in a human. While the NOD mouse is an acceptable animal model for human Type I diabetes, the showings of the specification must bear some correspondence to that which is claimed. Should applicants claim a method of suppression of insulitis in a human comprising the oral administration of glucagon and compositions therefore, the claims would be enabled. The specification supports such claims. However, the claims are not so drawn. As previously set forth, the skilled artisan would have reason to doubt that the differences in chemical composition and mode of administration would unpredictably effect the outcome because: Mueller et al (The Journal of NIH Research, 6:,47-51, October 1994) clearly indicates that "....the dose, chemical, physical form, route and frequency of administration, inflammatory capacity, or immunogenicity of the immunizing preparation act in concert to determine whether the immune responsiveness to an antigen will be enhanced or reduced as a result of immunization." (page 48, column 1, first full paragraph). Mueller et al also teaches that "T cell tolerance in vivo can depend on the regulation of T cell antigen responsiveness." and concludes that "..our ability to translate these data into a curative therapy for such diseases is hindered by gaps in our knowledge. It is difficult to predict what effect anergy induction might have on the behavior of autoimmune T cells because little information is available regarding the effect of anergy on T cell effector functions -- as opposed

to its generally accepted ability to block the clonal expansion of T cells. This is an important issue because, in the clinic, patients tend to be treated only after evidence of autoimmune disease has appeared." (pages 49-50, see bridging paragraph). Thus, the art teaches that it is difficult to predict the outcome for any particular antigen form for any specific autoimmune disease given that the autoimmune disease is already in progress in the clinic. Applicants have not demonstrated prevention or prophylaxis in the NOD mouse via an oral or nasal route, much less a human where the timing of the disease trigger is not known. Applicants have not taught that administration by nose suppresses insulitis in a NOD mouse, much less a human. Applicants' specification and evidence clearly does not speak to nasal administration of any bystander antigen which is not an autoantigen or not insulin. Applicants' continued reliance on oral administration of self antigens, is not germaine to the claimed subject matter. The reliance on this evidence clearly misdirects the issue in this application, because self antigens (i.e. the instant autoantigens or sensitized T-cells) are specifically excluded by the claims. Applicants' indicate insulin evidence on "newly diagnosed" individuals is relevant to manipulation of an ongoing autoimmune response and relevant to treatment if Type I diabetes in newly diagnosed individuals. This evidence is not persuasive because insulin is (a) specifically excluded by the claims and does not address a bystander antigen which is not an autoantigen or sensitized T-cells and (b) is not relevant to prevention or prophylaxis because these individuals already have the disease, thus prevention or prophylaxis can not be achieved. Unfortunately, because applicants have defined treatment in the specification to include prevention or prophylaxis, they have presented claims drawn to "treatment" which clearly encompasses more embodiments that are not enabled(i.e., prophylaxis, prevention), than are (i.e. suppression of insulitis). The examiner has presented Mueller et al which teaches the unpredictably of antigen to antigen and

route and dose of administration in achieving tolerance (i.e. suppression of insulitis). Thus, nasal administration of insulin is not predictive of glucagon. Applicants' have provided no evidence that nasal or oral glucagon prevents Type I diabetes, reduces need for insulin, decreases other symptoms of the disease, or prevents disease all of which are included in the term "treatment" as specifically defined in the specification. Thus, the examiner has established that applicants have written description for a single embodiment within the genus claims, that treatment via the means of oral tolerization is unpredictable (Mueller et al of record), depends on antigen, route of administration etc and that the scope of the claimed subject material does not warrant the enablement of the breadth of the claims. Applicants' argue that the rejections are set forth with excess rigor. Not so, the rejections are based upon facts as set forth by the examiner and reiterated above. The examiner has established a *prima facie* case for non-enablement at the time of that the invention was made (i.e. the filing date of the instant application). Applicants indicate that the data from in vitro and animal testing are generally sufficient to support therapeutic utility. While this may be true in a highly developed field, the field of applicants invention is highly unpredictable for the reasons set forth above. In an unpredictable field, more is required. Moreover, the MPEP states "generally", not always acceptable. Applicants' presented and attempt to rely on a plethora of evidence, none of which is germaine to the claimed subject matter for reasons set forth above. Applicants' have enabled a single embodiment within the scope of treatment of Type I diabetes with oral glucagon, suppression of insulitis. This single embodiment is not claimed nor presented in any of the dependent claims for consideration by the examiner. Applicants' have not enabled the breadth of treatment of autoimmune disease in a human by using a bystander antigen which is not an autoantigen or not insulin, nor have enabled treatment of Type I diabetes for reasons made of record. The scope of

the claims must be a reasonable correlation with the scope of enablement *(In re Fisher* 166 USPQ 1924 (CCPA 1970)), clearly here is does not, and applicants are not claiming an enabled embodiment.

The rejection is maintained.

5. The provisional rejection of claims 37-39, 42-45, 47-49, 52-59, 61, 62, 65 and 65 as previously applied to claims 37-45, 47-55, and 57 as being obvious over 08/461,591 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

6. The provisional rejection of claims 37-39, 42-45, 47-49, 52-59, 61, 62, 65 and 65 as previously applied to claims 37-58 as being obvious over 08/461,662 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

7. The provisional rejection of 37-39, 42-45, 47-49, 52-59, 61, 62, 65 and 65 as previously applied to claims 37-46 and 48-58 as being obvious over 08/468,996 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

8. The rejection of claims 61 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons made of record in Paper No. 13, mailed 2/28/98.

Applicants assert that this term is conventional in the art. This is not persuasive because there is *no definition in the art nor in the specification*, of what encompasses "substantially" in regard to purity or free from autoantigens. Thus, the metes and bound of the claims can not be ascertained.

The rejection is maintained.

New Rejections

9. Claims 47 and 59 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Tobin et al (U.S. Patent No. 5,475,086) is maintained for reasons made of record.

Tobin et al teach the administration of GAD-65 and fragments thereof as a treatment of autoimmune diseases involving GAD-65 and type I diabetes. Tobin et al teach GAD-65 and fragments thereof in a pharmaceutical carrier for administration in the treatment GAD autoimmune responses such as type I diabetes. Tobin et al teach effective dosages for the treatment using GAD-65 and fragments thereof (see columns 11-12) in a pharmaceutically acceptable carrier.

10. Claims 47 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tobin et al (U.S. Patent No. 5,475,086).

Tobin et al differs by not tableting or capsulating the GAD and fragments in a solid dosage pharmaceutical composition for intracavity administration (i.e. nasal, oral, rectal or enteric). However, it would have been *prima facie* obvious to one of ordinary skill in the art to provide a solid dosage form such as a tablet, micro encapsulate, capsule, comprising the GAD-65 polypeptide for *intracavity* administration, because Tobin et al teach that diabetes can be treated using the GAD-65 polypeptide by intracavity administration and the tableting and

encapsulation of drugs for intracavity administration is routine in the art of pharmaceutical preparation of intracavity agents.

Status of Claims

11. All claims stand rejected.

12. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
March 27, 2000

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600